

LISTING OF THE CLAIMS

Claim 1 (**currently amended**) A method for the production of a single heavy chain antibody in a transgenic non-human mammal comprising the step of expressing a heterologous VHH heavy chain locus in that mammal specifically in B cells in response to antigen challenge, wherein the VHH heavy chain locus comprises:

(a) at least one VHH exon, at least one D exon and at least one J exon, wherein the VHH exon, the D exon and the J exon are capable of recombining to form VDJ coding sequence, and wherein the VHH exon comprises a VHH coding sequence,

(b) a constant heavy chain region comprising at least one C $\mu$  constant heavy chain gene and at least one of C $\gamma$ , C $\alpha$ , C $\epsilon$ , or C $\delta$  constant heavy chain gene, wherein each of said constant heavy chain genes, when expressed, does not express a functional CH1 domain,

(c) a [[regulatory sequence]] locus control region ("LCR") providing for expression of the VHH heavy chain locus specifically in B cells

said method comprising:

- 1) immunizing said mammal with an antigen and
- 2) isolating single heavy chain antibody against said antigen from said mammal.

Claim 2 (**canceled**)

Claim 3 (**currently amended**) A method for the production of a single heavy chain antibody in a transgenic non-human mammal comprising the step of expressing a camelised VH heavy chain locus in that mammal specifically in B cells in response to antigen challenge, wherein the camelised VH heavy chain locus comprises:

- (a) at least one VH exon which is mutated such that, when expressed, the

resulting single heavy chain antibody is stabilised, at least D exon and at least one J exon, wherein the VH exon, the D exon and the J exon are capable of recombining to form VDJ coding sequence, and wherein the VH exon comprises a VH coding sequence and

(b) a constant heavy chain region comprising at least one C $\mu$  constant heavy chain gene and at least one of C $\gamma$ , C $\alpha$ , C $\epsilon$ , or C $\delta$  constant heavy chain gene, wherein each of said constant heavy chain genes, when expressed, does not express a functional CH1 domain,

(c) [[a regulatory sequence]] an LCR providing for expression of the VH[[H]] heavy chain locus specifically in B cells

said method comprising:

- 1) immunizing said mammal with an antigen and
- 2) isolating single heavy chain antibody against said antigen from said mammal.

Claims 4 – 6 (**canceled**)

Claim 7 (**currently amended**) [[A]] The method according to of claim 1 wherein the VHH single heavy chain locus comprises a camelid VHH, at least one D exon of human origin and at least one J exon of human origin and a constant region of human origin.

Claim 8 (**currently amended**) [[A]] The method according to of claim 3 wherein the camelised VH heavy chain locus comprises at least one D exon of human origin and at least one J exon of human origin and a constant region of human origin.

Claim 9 (**canceled**)

Claim 10 (**currently amended**) [[A]] The method according to of claim 1 or 3 wherein the constant heavy chain region comprises at least one constant region heavy chain gene which is of non-camelid origin.

Claim 11 (**original**) A method according to claim 10 wherein at least one constant region heavy chain gene is of human origin.

Claims 12 – 16 (**canceled**)

Claims 17 -32 (**canceled**)

Claim 33 (**previously presented**) The method of claim 1 wherein the entire VHH single heavy chain locus is of camelid origin

Claim 34 (**previously presented**) The method of claim 3 wherein the camelised VH single heavy chain locus is of human origin.

Claim 35 (**previously presented**) The method of claim 3 wherein the camelised VH single heavy chain locus is of non-human origin.

Claim 36 (**previously presented**) The method of claim 3 wherein the camelised VH single heavy chain locus is of camelid origin.

Claims 37 -38 (**canceled**)

Claim 39 (**previously presented**) The method according to claim 1 or 3 wherein the non-human mammal is a rodent.

Claim 40 (**canceled**)

Claim 41 (**new**) A method for the production of a single heavy chain antibody in a transgenic mouse comprising expressing a heterologous VHH heavy chain locus in that mammal specifically in B cells in response to antigen challenge wherein the VHH heavy chain locus comprises:

(a) at least one VHH exon, at least one-D exon and at least one-J exon, wherein the VHH exon, the D exon and the J exon are capable of recombining to form VDJ coding sequence, and

wherein the VHH exon comprises a VHH coding sequence, and

(b) a a constant heavy chain region comprising at least one C $\mu$  constant heavy chain gene and at least one of C $\gamma$ , C $\alpha$ , C $\epsilon$ , or C $\delta$  constant heavy chain gene, wherein each of said at least one constant heavy chain gene, when expressed, does not express a functional CH1 domain,

(c) a regulatory sequence providing for expression of the VHH heavy chain locus specifically in B cells

said method comprising:

- 1) immunizing said mammal with an antigen and
- 2) isolating single heavy chain antibody against said antigen from said mammal.

Claim 42 (**new**) A method for the production of a single heavy chain antibody in a transgenic mouse comprising expressing a camelised VH heavy chain locus in that mammal specifically in B cells in response to antigen challenge wherein the camelised VH heavy chain locus comprises:

(a) at least one VH exon which is mutated such that, when expressed, the resulting single heavy chain antibody is stabilised, at least one D exon and at least one J exon, wherein the VH exon, the D exon and the J exon are capable of recombining to form VDJ coding sequence, and wherein the VH exon comprises a VH coding sequence that has been mutated to be the same as the respective Camelid coding sequence, and

(b) a constant heavy chain region comprising at least one C $\mu$  constant heavy chain gene and at least one of C $\gamma$ , C $\alpha$ , C $\epsilon$ , or C $\delta$  constant heavy chain gene, wherein each of said at least one constant heavy chain gene, when expressed, does not express a functional CH1 domain,

(c) a regulatory sequence providing for expression of the VHH heavy chain locus

specifically in B cells

said method comprising:

- 1) immunizing said mammal with an antigen and
- 2) isolating single heavy chain antibody against said antigen from said mammal.